New Drug Candidates and Innovation for HAT:

From Discovery to Promising Candidates, Illustrated by Oxaboroles Development

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DNDi

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Neglected Diseases and Innovation

- Innovation in Neglected Diseases cannot be created with only “old” compounds
  - Combinations, new formulations, repurposing…
  - Toxicity, resistance, drug-drug interference, compliance…
- New drugs have to be discovered
  - New modes of action (resistance)
  - Safe (toxicity)
  - Easy-to-use (compliance)
  - Cheap (COGs)
- DND*i*: created HAT Lead Optimization Consortium in 2007
  - SCYNEXIS: center piece

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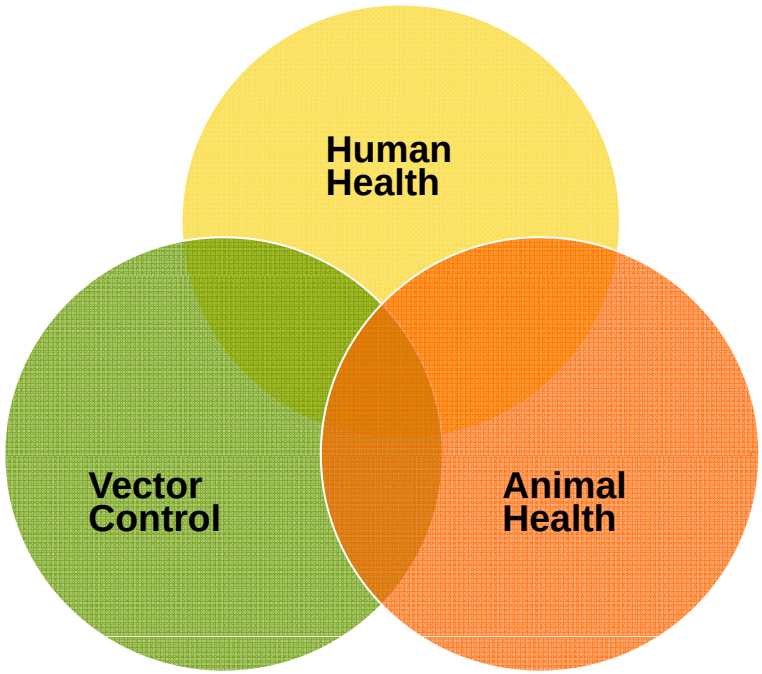
SCYNEXIS

An Integrated Parasitology Research Group



- **Expertise in early discovery, lead optimization and pre-clinical development**
  - Integrated medicinal chemistry, biochemistry, biology and ADMET-DMPK teams
  - Currently have 3 infectious disease compounds in clinical development
- **Core business built on partnerships with PPP's, Biotech, Pharma, Animal Health companies**
  - Screening paradigms targeting key NTD therapeutic areas
  - Internal expertise built through multi-year research programs for animal health and neglected disease discovery
  - Finding value for partners via the integrated parasitology expertise

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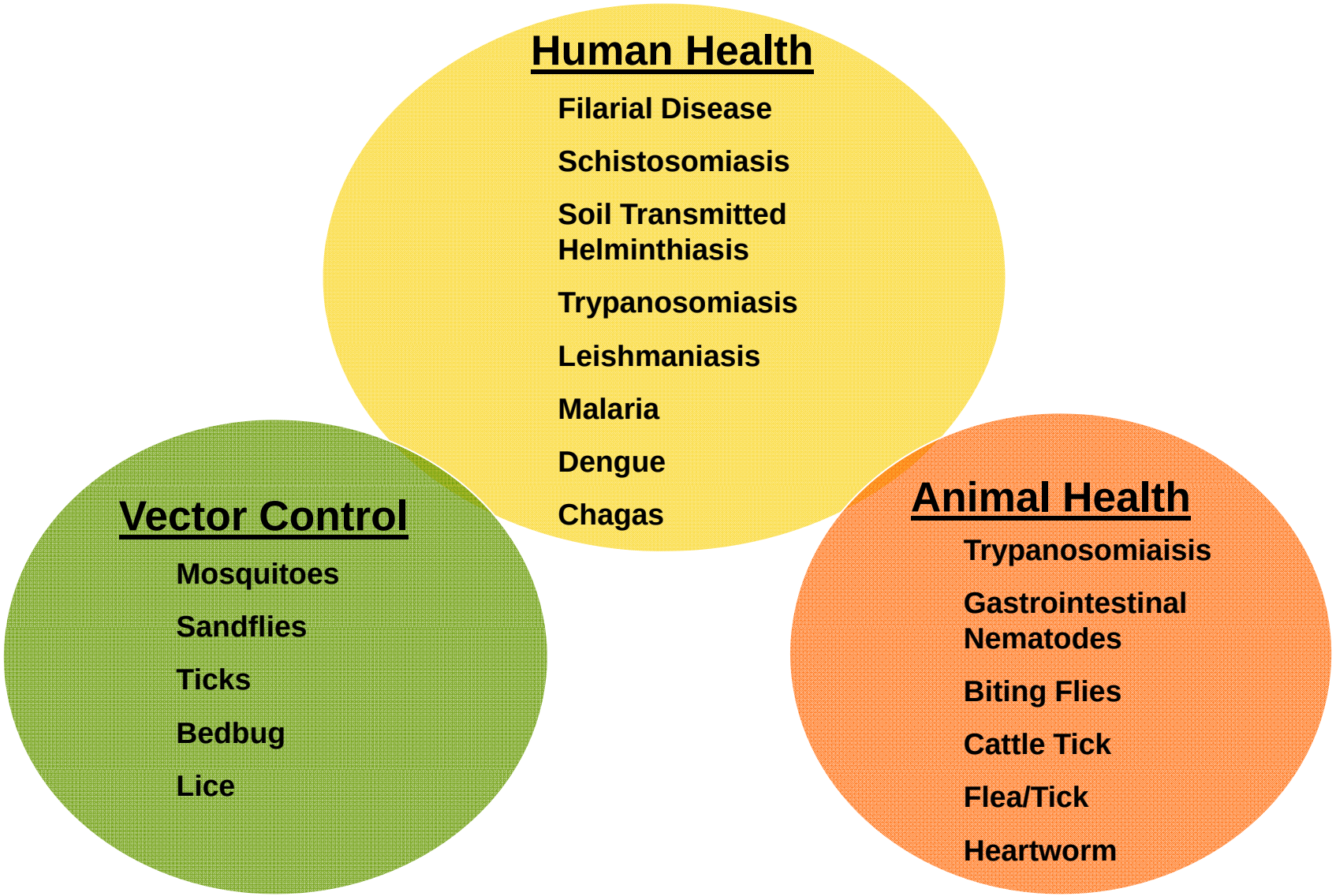
SCYNEXIS Integrated Parasitology Discovery Platform



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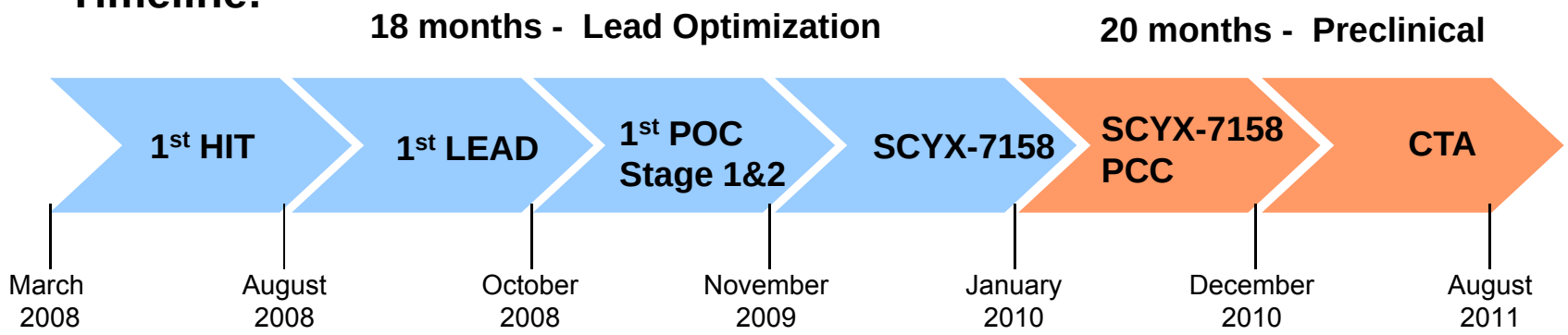
What It Takes: People, Time and Money

- **People fully dedicated to HAT project : 19**
  - **DND*i*:** 2 Project management
  - **SCYNEXIS**: 15
    - 7 Chemists
    - 4 Drug Metabolism and Pharmacokinetics
    - 3 Biologists
    - 1 Project Leaders
  - **Haskins Laboratories, Pace University**: 2 Biologists

- **Timeline:**



Among the best in industry

- **Money**
  - **$15 Million over 3 years**

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What It Takes: Partners

- **SCYNEXIS**: *In vitro T. b. brucei*, cytotoxicity, ADME assays; time-kill assays, bioanalysis
- **Haskins Laboratories, Pace Univ.**: *In vivo T. b. brucei* assays (Stage 1 and Stage 2)
- **Swiss Tropical and Public Health Institute**: *In vitro T. b. rhodesiense*, *T. b. gambiense* assays; *In vivo T. brucei* spp. assays (Stage 1 and Stage 2); Microcalorimetry studies
- **Advinus**: *In vivo* toxicology and safety pharmacology studies in rat and dog; GLP genotoxicity studies;
- **Anacor**: Profiling in antibacterial, antifungal and antiinflammatory assays
- **Drugabilis**: Physicochemical characterization (solubility, polymorphism)
- **Vivisource**: *In vivo* PK evaluation in mouse
- **Sinclair Research Laboratories**: *In vivo* PK evaluation in rat, dog
- **SNBL**: *In vivo* PK evaluation in cynomolgus monkey
- **Aptuit**: Synthesis of [14C]-SCYX-7158
- **BioReliance**: Non-GLP genotoxicity studies of SCYX-7158 and potential impurities
- **Cellular Dynamics**: Non-GLP hERG electrophysiology study
- **MDS Pharma Services**: Receptor, enzyme and ion channel profiling
- **Penn Pharma**: Formulation of drug product for Ph 1 clinical trial
- **Prof. S. Benkovic, Penn State Univ.**: pKa Determination
- **Prof. M. Ferguson, Univ. of Dundee**: MOA studies in *T. b. brucei*
- **Prof. M. Barrett, Glasgow Univ.**: Metabolomics studies in *T. b. brucei*

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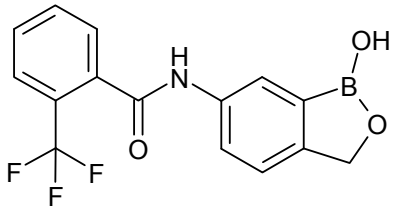
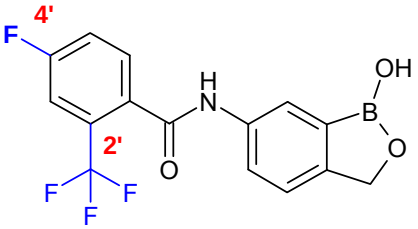
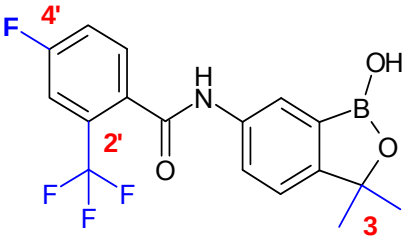
Benzoxaborole Series Progression



AN3520



SCYX-6759



SCYX-7158

- C(6) Carboxamides - Anacor
  - Provide high potency
  - Overcome limitations of sulfoxide (AN2920)
    - Stereochemistry
    - Metabolism to sulfone
- C(2') Substitution
  - Enhances potency, PK and brain disposition
  - Trifluoromethyl, chloro preferred
- C(4') Substitution
  - Blocks oxidative metabolism of benzamide
  - Enhances bioavailability
  - Increases brain disposition
  - Fluoro preferred
- C(3) Substitution
  - Enhances PK, brain disposition
  - Monosubstitution compromised by cytotoxicity
  - Potency decreased by more sterically demanding substituents

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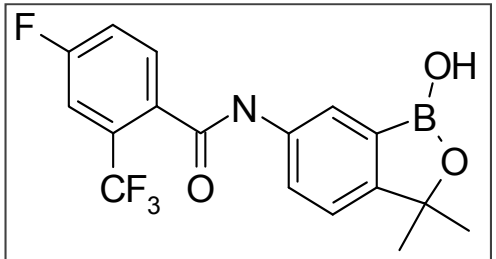
SCYX-7158: Profile of an Orally-Active Stage 1 & 2 HAT Drug Candidate*



SCYX-7158

In vitro activity vs.Trypanosoma brucei:

IC_{50} = 0.2 – 1.1 µM (including T.b. gambiense, T. b. rhodesiense)

Physicochemical properties:

logD = 3.51; aq. solubility = 25 µM

In vitro ADME properties:

Mouse, rat, human S9 $t_{1/2}$ > 350 min

MDCK-MDR1 P_{app} = 415 nm/Sec; AQ = 0.03

Curative of Stage 1 Murine HAT model @ 2.5 mg/kg, po, once-daily x 4 days

Curative of Stage 2 Murine HAT model @ 25 mg/kg, po, once-daily x 7 days

Excellent PK in mouse, rat, dog and cynomolgus monkey;

Excellent safety profile in rat and dog (28 day NOAEL = 15 mg/kg)

- Non-genotoxic, no hERG effects, clean safety pharmacology profile
- No evidence of irreversible binding to tissues, good tissue distribution (^{14}C)

Synthesized in 6 steps, no chromatography, crystalline API and intermediates

*Jacobs, R. T. etal. PLoS Negl. Trop. Dis. **2011**, 5, e1151.

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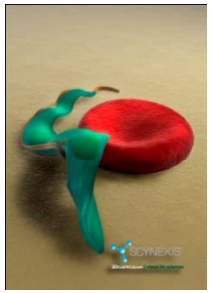

Building A HAT Pipeline

Discovery

- HAT LO Consortium

Preclinical

- Nitroimidazole
- Oxaborole →

Clinical

- Fexinidazole
- DDD85646 (Stage 1)
- CPD-0801 (Stage 2)

HCV

- 12 Proteases
- 14 Non-nucleotides
- 8 Nucleotides
- 6 Others

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